II. REMARKS

Claims 47 to 67 are pending in the subject application and stand variously rejected by the U.S. Patent and Trademark Office. This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented above with an appropriate defined status identifier. Specifically, claims 47, 48, 50, 52 to 54, 56 to 67 have been amended and claims 49, 51 and 55 have been canceled without prejudice or disclaimer to Applicants' right to file the same or similar claims in a later filed application.

The amendments to the claims do not raise an issue of new matter. Claims 52, 53, 54, 59-60, 62, 66 and 67 have been amended to correct grammatical errors. Claim 56 has been amended to correct a dependency.

Support for the amendments to claims 47, 48 and 57 is found in the application on page 6, lines 6 to 14; page 7, lines 16 to 27 and page 14, line 2.

Amended claim 50 is supported on page 7, lines 16 to 27.

Amended claim 58 is supported on page 9, lines 16 to 27.

Amended claim 61 supported on page 8, line 5.

Support for the amendment to claim 63 is found on page 8, line 5.

Support for the amendment to claim 64 is found on page 8, line 5; page 6, lines 21 to 24 and page 15.

These amendments were not made earlier as it is Applicants' position that the claims as previously presented satisfied the requirements of patentability. The amendments are being made at this time in a sincere effort to place the application in condition for allowance or in better form for consideration on appeal.

After entry of the amendments, claims 47 to 49, 51 to 54, 56 to 67 are pending and under examination. In view of the preceding amendments and the remarks which follow, reconsideration and withdrawal of the rejections are respectfully requested.

35 U.S.C. § 102

Claims 57 to 59 remain rejected under 35 U.S.C. § 102, as allegedly anticipated by New England Biolabs Catalog (1996, page 102) (hereinafter "Biolabs Cat."). The Office argued that the Biolab Catalog teaches a kit containing a DNA ladder X174 DNA-Hae III Digest that contains base pairs in the order of 1,353 base pairs to 72 base pairs. The Office noted that alternatively, Biolab Cat. teaches a kit that contains a DNA ladder pBR322 DNA-BstN I Digest that contains base pairs on the order of 1,857 to 13 base pairs. The Office argued that either of the DNA ladders could be used as sequencing markers and appear to be a component of the kit of claim 58. Additionally, the Office noted that the DNA is provided in a solution of 10 mM Tris and 1 mM EDTA.

The Office also stated that Applicants' prior remarks were unpersuasive because the elements that Applicants rely on to distinguish the invention were not recited in the claims, specifically a genomic polymorphism in the 5' UTR. The Office also stated that Applicants' assertion with regard to the cited art for failing to provide instructions for the kit have been review but were not persuasive because the components of the kit could be used for other purposes.

Applicants respectfully traverse. Amended claims 57 is directed to a kit for use in screening for the effectiveness of thymidylate synthase (TS) directed drug therapy in human subjects, the kit comprising: a means for detecting a tandemly repeated 28 bse pair sequence in the 5' UTR of the TS gene and instructions for correlating the genomic polymorphism of the 5' UTR of the TS gene to sensitivity to TS directed drug therapy. Amended claim 58 is directed to the kit of claim 57, but further containing one or more of positive controls, negative controls, reagents, or sequencing markers. Amended

claim 59 is directed to the kit of claim 57 wherein the components may be provided in solution or as a liquid dispersion.

The Biolab Cat. fails to anticipate these claims because it fails to provide a means for identifying the specific polymorphism recited in amended claim 57. For this reason, the rejection is improper and therefore should be removed.

Claims 47 to 50, 61, 62 and 64 to 66 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Horie. The Office argued that Horie teaches a method of analyzing the DNA polymorphism of the tandemly repeated sequences in the 5' terminal regulatory region of the TS gene in genomic DNA from leukocyte samples from normal patients.

Applicants respectfully traverse. Claim 49 has been canceled. Independent and amended claim 47 and dependent claims 48 to 50, 61, 62 and 64 to 66 are directed to a method for screening a subject for sensitivity to a thymidylate synthase (TS) – directed chemotherapeutic drug by determining the genotype of the subject's biological sample at a tandemly repeated 28 base pair sequence in the 5' untranslated region (UTR) of a TS gene in the sample and correlating said genotype to said sensitivity to TS – directed chemotherapy. Horie et al. notes that there exists a polymorphism in the 5'UTR of the TS gene which may influence mRNA expression level. However, in the Discussion section of the paper, the authors clearly state that no conclusions can be drawn from their initial finding:

> "A difference in the actual number of specific repeated sequences is known to be related to certain inherited diseases. However, the polymorphism in the repeated sequences in the 5'-terminal region of the hTS gene was detected among normal human individuals and at present, there are no data to suggest that the polymorphism might be related to any abnormal physical condition. Taking into account the essential role of the TS enzyme in biological systems, we find it interesting that the DNA polymorphism in the hTS gene seemed to have no effect on the physical

> condition of the individuals from which the genes were isolated, although the expression of the reporter gene linked to the polymorphic region of the hTS gene with its promoter depended on the structure of the polymorphic region in the transient expression assay. At present, it is not clear whether the polymorphism-related difference in the transient expression assay affects the biological systems that involve the TS enzyme. Further studies are needed to clarify the effects of the variable number of repetitions in the unique structure of the hTS gene on biological systems."

Page 196, first full paragraph of column 2, citations omitted.

For this reason, the rejection is made in error and its withdrawal is respectfully requested.

Claims 47, 48 and 61-66 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Govindarajan. The Office argued that Govindarajan teaches a method using PCR to genotype the GSTM1 gene from peripheral blood cells in patients with lung cancer who had received 3 cycles of platinum based chemotherapy. The Office also argued that the reference teaches that there was a higher incidence of GSTM1 null genotypic expression in patients with small cell cancer responders as opposed to non-small cell lung cancer responders.

Claims 47, 48 and 61 to 66 were rejected under 35 U.S.C. § 102 (a) and (b) as allegedly anticipated by Howells. The Office cited the reference for teaching a method of correlating GSTT1 null and GSTM1 null genotypes to unresponsiveness to primary chemotherapy in patients with epithelial ovarian cancer. Howells also was cited for teaching genotyping for the null alleles using PCR on DNA isolated from blood or tissue identified as macroscopically normal by the surgeon for genotyping. Howells was also cited for teaching that null alleles for both GSTT1 and GSTM1 was associated with nonresponsiveness to chemotherapy.

Applicants respectfully traverse. The amended claims are directed to a specific polymorphism in the 5' UTR of the TS gene. Govindarajan and alternatively Howells teach a polymorphism in a different gene. Thus, the references do not teach each and every element of the rejected claims. Accordingly, removal of the rejections as applied against these claims is respectfully requested.

35 U.S.C. § 103

Claims 47 to 56 and 61 to 67 stand rejected under 35 U.S.C. § 103 (a) for allegedly being non-obvious over the combination of Horie and Leichmann in view of Ruano and further in view of, or in the alternative, Govindarajan or Howells. For the sake of brevity, the stated grounds for rejection of the claims will not be repeated here as they encompass three and one-half pages of the Office Action.

Applicants respectfully traverse. The Examiner fails to present a *prima facie* case of obviousness of the rejected claims. None of the references teaches or suggests that the presence of this genetic polymorphism, in the 5 'UTR of the TS gene and its relationship to chemotherapeutic response. Although Horie identifies a TS polymorphism in the 5' UTR of the TS gene, neither Horie nor any of the secondary or tertiary references correlate this polymorphism to therapeutic effect or pathology. At best, the secondary references indicate a desirability to identify polymorphisms in genes other than TS and where possible, the correlation of the polymorphisms with therapeutic response. This at best, is an invitation to experiment and which fails to rise to the level of motivation to combine. The invitation to experiment has never been sufficient grounds to hold an invention obvious over the prior art. *See In re Dow Chemical Co. v. American Cyanamid Co.*, 837 F.2d 469, 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988) (in reversing the Board's finding of obviousness, the Federal Circuit noted that that the prior art must provide some reason or suggestion for selecting the Board's proposed procedure).

In addition, the Office did not consider the art as a whole that includes the express teaching away present in the Horie et al. publication. For example, Horie et al. stated:

> "A difference in the actual number of specific repeated sequences is known to be related to certain inherited diseases. However, the polymorphism in the repeated sequences in the 5'-terminal region of the hTS gene was detected among normal human individuals and at present, there are no data to suggest that the polymorphism might be related to any abnormal physical condition."

Horie et al., Page 196 first full paragraph of the second column.

Thus Applicants submit that the teachings of the references as a whole fail to provide a *prima facie* case of obviousness. Accordingly, removal of the rejection is respectfully requested.

The claims directed to a kit, *i.e.*, claims 57 to 60, were also rejected as allegedly obvious over the combination of Horie and Leichman in view of Ruano, and further in view of Govindarajan or Howells, as applied to claims 47 to 56 and 61 to 67, above, and yet further in view of Erlich (U.S. Patent No. 5,468,613). The Office acknowledged that the teachings of Horie and Leichman in vie wof Ruano, and further in view of Govindarajah or Howells do not teach a kit comprising DNA tandemly repeated sequences of the TS gene; however, Erlich was cited for teaching constructing allele specific probes for the purpose of identifying specific alleles in hybridization assays. The Office also argued that Erlich kits which include sequence specific oligonucleotides and that therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to construct sequence specific oligonucleotides as taught by Erlich that contained tandemly repeated sequences of the TS gene for use in the method of Horie and Leichman, in view of Ruano and further in view of Govidnarajan or

Howells for the purpose of providing a sequence specific oligonucleotide that could be used to determine a subject's TS genotype in the screening method of Horie and Leichman. The Office further stated that the ordinary artisan would have been motivated to provide such an oligonucleotide kit format for the obvious improvement of pre-weighed, premeasured reagents that would make the method of Horie and Leichman, in view of Ruano, and further in view Govidnarajan or Howells more convenient to perform.

Applicants respectfully traverse. Claims 57 to 60 are directed to a kit for for use in screening for the effectiveness of thymidylate synthase (TS) directed drug therapy in human subjects, the kit comprising a means for determining a genomic polymorphism, if present, of a tandemly repeated 28 base pair sequence of the 5 'UTR of the TS gene and instructions for correlating the genomic polymorphism of the 5' UTR of the TS gene to sensitivity to TS directed drug therapy.

Claims 57 to 60 are non-obvious in view of the cited references for the same reasons noted above. The combination of references fails to provide a motivation to combine them in the manner the Office has to arrive at the rejection under 35 U.S.C. § 103. For this reason, the Office has failed to present a *prima facie* case of obviousness. The rejection is in error and therefore should be withdrawn.

III CONCLUSION

Applicants believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any

overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

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